(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 02/068438 A2

(51) International Patent Classification[7]: C07H 17/00

(21) International Application Number: PCT/HR02/00010

(22) International Filing Date: 27 February 2002 (27.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P20010146A 28 February 2001 (28.02.2001) HR

(71) Applicant *(for all designated States except US)*: **PLIVA D.D.** [HR/HR]; Ulica Grada Vikovara 49, HR-10000 Zagreb (HR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUJUNDZIC, Nedjeljko** [HR/HR]; Slavenskog 4, HR-10000 Zagreb (HR). **BUKVIC KRAJACIC, Mirjana** [HR/HR]; Slavenskog 8, HR-10000 Zagreb (HR). **DUMIC, Miljenko** [HR/HR]; Ivane Brlic Mazuranic 4, HR-10000 Zagreb (HR). **HASENOHRL, Andrea** [HR/HR]; Dragozetnicka 11, HR-10000 Zagreb (HR).

(74) Agent: **PLIVA D.D.**; Ulica Grada Vukovara 49, HR-10000 Zagreb (HR).

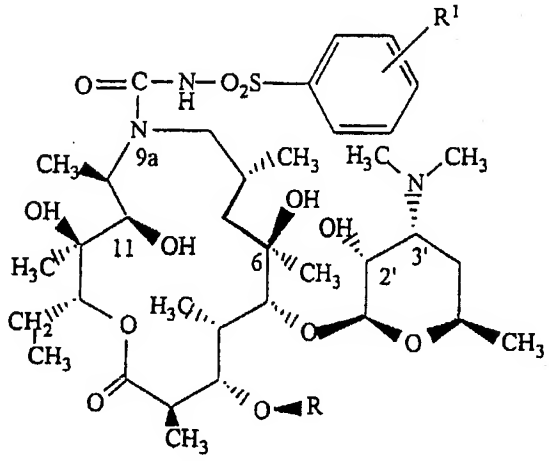
(81) Designated States *(national)*: AU, BA, CN, CZ, EE, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, PL, RO, SI, SK, TR, UA, US, YU, ZA.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 9A-N-[N'-(PHENYLSULFONYL)CARBAMOYL] DERIVATIVES OF 9-DEOXO-9-DIHYDRO-9A-AZA-9A-HOMOERYTHROMYCIN A AND OF 5-O-DESOSAMINYL-9-DEOXO-9-DIHYDRO-9A-AZA-9A-HOMOERYTHRONOLIDE A



(I)

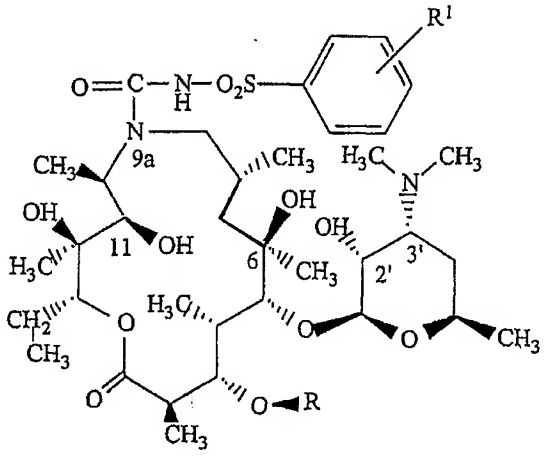
(57) Abstract: The invention relates to 9a-N[N'-(phenylsulfonyl)carbamoyl] derivatives of 9-deoxo-9-dihydro-9a-aza-homoerythromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A, novel semisynthetic macrolide antibiotics from the class of azalides, of the general formula 1 wherein R^1 denotes H, C_1-C_4alkyl or halogen and R denotes H or cladinosyl radical, to their pharmaceutically acceptable addition salts with inorganic or organic acids, to intermediates and methods for their preparation, to a process for the preparation of pharmaceutical compositions as well as to the use of pharmaceutical compositions in the treatment of bacterial infections.

WO 02/068438 A2

9a-N-[N'-(Phenylsulfonyl)carbamoyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A

IPC: C07H 17/08, A 61K 31/71

The invention relates to 9a-N-[N'-(phenylsulfonyl)carbamoyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A, novel semisynthetic macrolide antibiotics from the class of azalides with antibacterial action, shown by the general formula **1**



1

wherein R denotes H or cladinosyl radical and R^1 denotes H, C_1-C_4 alkyl or halogen, to their pharmaceutically acceptable addition salts with inorganic or organic acids, to a process for their preparation, to a process for the preparation of pharmaceutical compositions as well as to the use of the obtained pharmaceutical compositions in the treatment of bacterial infections.

Erythromycin A is a macrolide antibiotic, whose structure is characterized by a 14-membered macrolactone ring with a carbonyl group in C-9 position. It was discovered by McGuire in 1952 [Antibiot. Chemother., **2** (1952) 281] and has been for more than 40 years considered a safe and active antimicrobic agent in the therapy of

diseases caused by gram-positive and some gram-negative microorganisms. However, in an acidic medium it is easily converted into anhydroerythromycin A, an inactive C-6/C-12 metabolite of spiroketal structure [P. Kurath et al., Experientia **27** (1971) 362]. It is known that spirocyclisation of the aglicone ring of erythromycin A is successfully inhibited by a chemical transformation of C-9 ketone or hydroxyl groups in C-6 and/or C-12 positions. By the oximation of C-9 ketones [S. Đokić et al., Tetrahedron Lett., **1967**: 1945] and subsequent modification of the obtained 9(E)-oxime into 9-[O-(2-methoxyethoxy)methyloxime]erythromycin A (ROXYTROMYCIN) [G. S. Ambrieres, FR patent 2,473,525, 1981] or 9(S)-erythromycylamine [R. S. Egan et al., J. Org. Chem., **39** (1974) 2492] or into its more complex oxazine derivative, 9-deoxo-11-{imino[2-(2-methoxyethoxy-ethylidene]oxy}-9,8S)erythromycin A (DIRITHROMYCIN) [P. Lugar et al., J. Crist. Mol. Struct., **9** (1979) 329], there were synthesized novel semisynthetic macrolides, whose basic characteristics, in addition to a higher stability in an acidic medium, are better pharmacokinetics and a long biological half-life in comparison to the parent antibiotic erythromycin A. A third way for modification of C-9 ketones uses Beckmann rearrangement of 9(E)-oximes and a reduction of the obtained imino ether [G. Kobrehel et al., US patent 4,328,334, 1982] into 11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9-dihydro-9a-aza-9a-homoerthromycin A) by enlarging the 14-membered ketolactone ring into a 15-membered azalactone ring. By a reductive N-methylation of 9a-amino group according to Eschweiler-Clark process [G. Kobrehel et al., BE patent 892,397, 1982] or preliminary protection of the amino group by conversion into corresponding N-oxides and subsequent alkylation and reduction [G. M. Bright, US patent 4,474,768, 1984], there was synthesized N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9-dihydro-9a-methyl-9a-aza-9a-homoerythromycin A, AZITHROMYCIN), a prototype of azalide antibiotics which are, in addition to having a wide antimicrobial spectrum including gram-negative bacteria and intracellular microorganisms, also characterized by a specific mechanism of transport to the application site, long biological half-life and short time of therapy. EP patent 0316128 (G. M. Bright) describes novel 9a-allyl- and 9a-propargyl derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and US patent

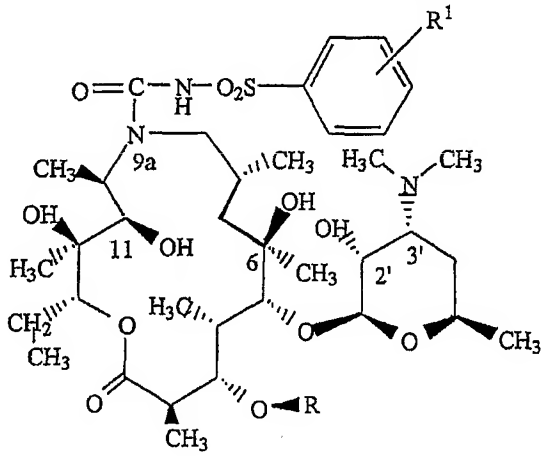
4,492,688 (1985, G. M. Bright) are described syntheses and antibacterial action of corresponding cyclic ethers. G. Kobrehel et al., J. Antibiot., 46 (1993) 1239-1245, further describe the synthesis and action spectrum of novel 9-deoxo-9-dihydro-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamates and their O-methyl derivatives.

By a reaction of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A with isocyanates or isothiocyanates respectively (N. Kujundžić, G. Kobrehel, Ž. Kelnerić, HR patent 931480, 1993), 9a-N-(N'-carbamoyl)- and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A with a certain antibacterial activity are obtained.

It has been found - and this represents a subject of the present invention - that compounds of the general formula **1**, novel semisynthetic macrolide antibiotics from the class of azalides, and their pharmaceutically acceptable addition salts with inorganic or organic acids can be prepared by a reaction of 9-deoxo-9a-aza-9a-homoerythromycin A or 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homo-erythronolide A of the general formula **2** with phenylsulfonylisocyanates and, if necessary, by a reaction of the obtained 9a-N-[N'-(phenylsulfonyl)carbamoyl derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A with inorganic or organic acids.

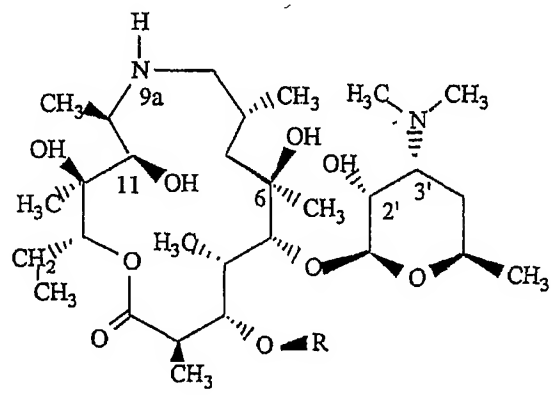
According to the known and established prior art, 9a-N-[N'-(phenylsulfonyl)carbamoyl derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homo-erythromycin A and of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homo-erythronolide A and their pharmaceutically acceptable addition salts with inorganic or organic acids, a process for their preparation and methods of preparation and of use as pharmaceutical compositions have hitherto not been described.

It has been found that novel 9a-N-[N'-(phenylsulfonyl)carbamoyl-derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A of the general formula **1**



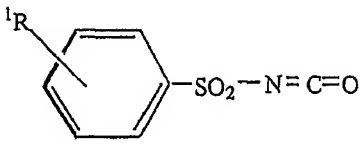
1

wherein R in R^1 have the above meanings, and their pharmaceutically acceptable addition salts with inorganic or organic acids may be prepared by reacting 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A or 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A of the general formula **2**, wherein R represents H or a cladinosyl radical



2

with phenylsulfonylisocyanates of general formula **3**



3

wherein R^1 has the above given meanings, in toluene, xylene or some other aprotic solvent, at a temperature from 0°C to 110°C in a time required for a complete conversion of the starting compound **2**, preferably from 0.5 to 10 hours.

Pharmaceutically acceptable addition salts, which are also a subject of the present invention, are obtained by a reaction of 9a-N-[N'-(phenylsulfonyl)carbamoyl derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A of the general formula **2** with an at least equimolar amount of a corresponding inorganic or organic acid such as hydrochloric, hydroiodic, sulfuric, phosphoric, acetic, trifluoroacetic, propionic, benzoic, benzenesulfonic, methanesulfonic, laurylsulfonic, stearic, palmitic, succinic, ethylsuccinic, lactobionic, oxalic, salicylic and similar acids, in an inert solvent. The addition salts are isolated by evaporation of the solvent or, alternatively, by filtration after spontaneous precipitation or by precipitation by the addition of a non-polar co-solvent.

9a-N-[N'-(Phenylsulfonyl)carbamoyl derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homo-erythronolide A of the general formula **1** and their pharmaceutically acceptable addition salts with inorganic or organic acids possess antibacterial *in vitro* activity. Minimal inhibitory concentrations (MIC, in μg/ml) are determined by dilution method on microplates according to recommendations of National Committee for Clinical Laboratory Standards (NCCLS, M7-A2). So e.g. the minimal inhibitory concentration on *Streptococcus pneumoniae* ATCC 6305 for the compounds from Examples 1 and 4 is 2 μg/ml and for compounds from Examples 2 and 3 is 1 μg/ml. Thus, they can be used for disinfection of rooms, surgical instruments and people as well as therapeutic agents in the treatment of infective diseases in animals, specially mammals, or humans

that are caused by a wide spectrum of gram-positive bacteria, microorganisms or generally pathogenic microorganisms which are sensitive to the compounds of the formula **1**. For this purpose the above compounds or their pharmaceutically acceptable salts with acids may be used orally in usual doses from 0.2 mg/kg body weight per day to about 250 mg/kg/day, most frequently from 5-50 mg/kg/day, or parenterally in the form of subcutaneous or intramuscular injections.

A process for the preparation of the compounds of the present invention is illustrated by the following examples which in no way limit the scope of the invention.

Example 1

9-Deoxo-9-dihydro-9a-N-[N'-(4-chlorobenzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromycin A

9-Deoxo-9-dihydro-9a-aza-homoerythomycin A (3.38 g, 0.0046 moles) was dissolved in toluene (40 ml) and 4-chlorobenzensulfonylisocyanate (about 1.0 g, 0.0046 moles) was added at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of pure 9-deoxo-9-dihydro-9a-N-[N'-(4-chlorobenzene-sulfonyl)carbamoyl]-9a-aza-9a-homoerythromycin A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol : ammonia = 90 : 9 : 1.5.

IR (KBr)/cm^{-1}: 1728, 1579, 1556, 1126, 1013.

^{1}H NMR (500 MHz, DMSO)/δ: 4.46 (1H, H-1'), 4.91 (1H, H-1"), 3.93 (1H, H-3), 3.46 (1H, H-5), 3.34 (3H, 3"-OCH_3), 2.91 (1H, H-4"), 2.50 (6H, 3'-N'$(CH_3)_2$), 2.26 (1H, H-2"b), 1.52 (1H, H-2"a), 1.27 (1H, H-8), 1.23 (3H, 10-CH_3), 1.14 (3H, 3"-CH_3), 0.96 (3H, 4-CH_3), 0.82 (3H, H-5).
^{13}C NMR (500 MHz, DMSO)/δ: 177.1 (C-1), 154.6 (9a-NCONH), 101.4 (C-1'), 95.8 (C-1"), 82.6 (C-5), 77.2 (C-3), 48.7 (3"-OCH_3), 44.7 (C-2), 25.7 (C-8), 20.9 (8-CH_3), 12.2 (10-CH_3), 10.7 (C-15).

MS (ES^+) m/z (%): 952.5.

Example 2

9-Deoxo-9-dihydro-9a-N-[N'-(p-toluenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromycin A

Analogously to the process described in Example 1, 9-deoxo-9-dihydro-9a-aza-homoerythromycin A (3.88 g, 0.0051 moles) was dissolved in toluene (40 ml) and p-

toluenesulfonylisocyanate (1.04 g, 0.0053 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of pure 9-deoxo-9-dihydro-9a-N-[N'-(4-chlorobenzenesulfonyl)-carbamoyl]-9a-aza-9a-homoerythromycin A was perfomed by chromatography on a silica gel column in a solvent system methylene chloride : methanol = 1 : 1.

IR (KBr/cm^{-1}): 1731, 1644, 1556, 1126, 1013.

^{1}H NMR (500 MHz, pyridine)/δ: 8.22, 8.15, 7.18 (phenyl), 5.70 (9a-NCONH), 5.40 (1H, H-13), 5.37 (1H, H-1"), 5.01 (1H, H-1'), 4.81 (1H, H-3), 4.54 (1H, H-5"), 4.11 (1H, H-5), 4.03 (1H, H-5'), 3.67 (1H, H-2'), 3.47 (1H, 3"-OCH_3), 3.32 (1H, H-10), 3.24 (1H, H-4"), 3.13 (1H, H-2), 2.42 (1H, 3'-$N(CH_3)_2$), 2.18 (3H, R-CH_3), 1.96 (1H, 7a), 1.91 (1H, H-8), 1.82 (1H, H-7b), 1.51 (3H, 4-CH_3), 1.52 (1H, 5"-CH_3), 0.93 (3H, H-15).

^{13}C NMR (500 MHz, pyridine)/δ: 179.0 (C-1), 142.7 (9a-NCONH), 130.1, 127.9, 126.9 (phenyl), 103.8 (C-1'), 95.8 (C-1"), 84.7 (C-5), 79.2 (C-4"), 79.0 (C-3), 78.0 (C-13), 75.4 (C-6), 73.7 (C-12), 72.6 (C-11), 71.4 (C-2'), 68.4 (C-5'), 66.5 (C-5"), 58.3 (C-10), 50.0 (3"-OCH_3), 46.5 (C-2), 43.7 (C-7), 27.8 (C-8), 19.3 (5"-CH_3), 15.7 (2-CH_3), 14.3 (12-CH_3), 11.8 (C-15), 10.3 (4-CH_3).

MS (EI^+) m/z (%): 932.5.

Example 3

9-Deoxo-9-dihydro-9a-N-[N'-(o-toluenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromicyn A

Analogously to the process described in Example 1, 9-deoxo-9-dihydro-9a-aza-homoerythromycin A (3.73 g, 0.0051 moles) was dissolved in toluene (40 ml) and o-toluenesulfonylisocyanate (1.0 g, 0.0051 moles) was added dropwise at a

temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 9-deoxo-9-dihydro-9a-N-[N'-(o-toluenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromycin A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol : ammonia = 90 : 9 : 1.5.

IR (KBr)/cm^{-1}: 1727, 1633, 1556, 1126, 1013.

^1H NMR (500 MHz, DMSO)/δ: 7.77, 7.25, 7.14 (phenyl), 4.90 (1H, H-1'), 4.85 (1H, H-13), 4.44 (1H, H-1'), 4.01 (1H, H-5"), 3.47 (1H, H-5), 3.47 (1H, H-5), 3.69 (1H, H-5'), 3.25 (3H, 3"-OCH_3), 3.00 (1H, H-2'), 2.91 (1H, H-4"), 2.37 (3H, 3'-$N(CH_3)_2$), 2.27 (1H, H-2"a), 1.95 (1H, H-4), 1.52 (1H, H-2"b), 1.25 (1H, H-8), 1.17 (3H, 5"-CH_3), 1.09 (3H, 5'-CH_3), 0.96 (3H, 4-CH_3), 0.82 (3H, H-15).

^{13}C NMR (500 MHz, DMSO/δ: 178.0 (C-1), 102.7 (C-1'), 95.2 (C-1"), 83.2 (C-5), 78.2 (C-4"), 78.0 (C-3), 75.8 (C-13), 74.4 (C-6), 73.7 (C-12), 73.5 (C-3"), 71.0 (C-2'), 67.7 (C-5'), 65.8 (C-5"), 65.5 (C-3'), 51.6 (3"OCH_3), 45.7 (C-2), 42.8 (C-4), 40.1 (3'-$N(CH_3)_2$), 35.4 (C-2"), 30.9 (C-4'), 25.8 (C-8), 18.3 (5"-CH_3), 15.6 (12-CH_3), 11.9 (C-15), 10.0 (4-CH_3).

MS (EI^+) m/z (%): 932.8.

Example 4

9-Deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromicyn A

Analogously to the process described in Example 1, 9-deoxo-9-dihydro-9a-aza-homoerythromycin A (4.01 g, 0.0055 moles) was dissolved in toluene (40 ml) and benzenesulfonylisocyanate (1.0 g, 0.0055 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of

the pure 9-deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)carbamoyl]-9a-aza-9a-homo-erythromycin A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol : ammonia = 90 : 9 : 1.5.

IR (KBr)/cm^{-1}: 1719, 1638, 1551, 1126, 1011.

^{1}H NMR (500 MHz, DMSO)/δ: 7.84, 7.71, 7.54, 7.36 (phenyl), 4.77 (1H, H-1"), 4.44 (1H, H-1'), 4.01 (1H, H-5"), 3.21 (3H, 3"OCH_3), 2.90 (1H, H-4"), 2.49 (3H, 3'$N(CH_3)_2$, 2.26 (1H, (H-2"a), 1.76 (1H, H-14a), 1.51 (1H, H-2"b), 1.32 (1H, H-14b), 1.16 (3H, 5"-CH_3), 0.78 (3H, H-15).

^{13}C NMR (500 MHz, DMSO)/δ: 159.0, (9a-N-CO-NH), 128.8, 127.7, 126.3 (phenyl), 77.4 (C-4"), 72.7 (C-3"), 65.0 (C-5"), 49.0 (3"-OCH_3), 39.4 (3'-$N(CH_3)_2$), 35.1 (C-2"), 18.7 (5"-CH_3), 11.1 (C-15), 9.5 (4-CH_3).

MS (ES^+) m/z (%): 918.8.

Example 5

9-Deoxo-9-dihydro-9a-N-[N'-(2-chlorobenzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromicyn A

Analogously to the process described in Example 1, 9-deoxo-9-dihydro-9a-aza-homoerythromycin A (3.38 g, 0.0046 moles) was dissolved in toluene (40 ml) and 2-chlorobenzenesulfonylisocyanate (1.0 g, 0.0046 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 9-deoxo-9-dihydro-9a-N-[N'-(2-chlorobenzenesulfonyl)-carbamoyl]-9a-aza-9a-homoerythromycin A was performed by chromatography on a silica gel column first in a solvent system methylene chloride : methanol = 7 : 3 and then in a solvent system methylene chloride : methanol : ammonia = 90 : 9 : 1.5.

IR (KBr)/cm^{-1}: 1728, 1579, 1126, 1012.

^{1}H NMR (500 MHz, DMSO)/δ: 7.71 (phenyl), 5.08 (1H, H-13), 4.80 (1H, H-1"), 4.49 (1H, H-1'), 4.15 (1H, H-3'), 4.03 (1H, H-5"), 3.43 (1H, H-5), 3.22 (3H, 3"-OCH_3), 2.91 (1H, H-4"), 2.76 (1H, H-2), 2.50 (3H, 3'-$N(CH_3)_2$), 2.39 (1H, H-2"a), 1.14 (3H, 3"-CH_3), 0.88 (3H, H-15), 0.85 (3H, 12-CH_3).

^{13}C NMR (500 MHz, DMSO)/δ: 102.0 (C-1'), 97.0 (C-1"), 85.6 (C-5), 78.5 (C-4"), 68.0 (C-3'), 65.8 (C-5"), 45.2 (C-2), 40.5 (3'-$N(CH_3)_2$), 49.5 (3"-OCH_3), 35.6 (C-2"), 21.2 (3"-CH_3), 18.7 (5"-CH_3), 14.3 (12-CH_3), 10.8 (C-15).

MS (EI^+) m/z (%): 952.9

Example 6

9-Deoxo-9-dihydro-9a-N-[N'-(4-fluorobenzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromicyn A

Analogously to the process described in Example 1, 9-deoxo-9-dihydro-9a-aza-homoerythromycin A (1.46 g, 0.002 moles) was dissolved in toluene (20 ml) and a toluenic suspension of 4-fluorobenzenesulfonylisocyanate (0.4 g, 0.002 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 9-deoxo-9-dihydro-9a-N-[N'-(4-fluoro-benzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythromycin A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol = 7 : 3.

IR (KBr)/cm^{-1}: 1727, 1638, 1593, 1552, 1126, 1013.

^{1}H NMR (500 MHz, DMSO)/δ: 7.74, 7.71, 7.16 (phenyl, 4.78 (1H, H-1"), 4.45 (1H, H-1'), 4.01 (1H, H-5"), 3.21 (3H, 3"-OCH_3), 2.91 (1H, H-4"), 2.51 (3H, 3'-$N(CH_3)_2$),

2.27 (1H, H-2"a), 1.52 (1H, H-2"b), 1.17 (3H, 5"-CH_3), 1.14 (3H, 3"-CH_3), 0.94 (3H, H-15), 0.81 (3H, 4-CH_3).

^{13}C NMR (500 MHz, DMSO)/δ: 177.2 (C-1), 160.6 (9a-NCO), 101.1 (C-1'), 95,8 (C-1"), 84.1 (C-5), 77.2 (C-4"), 72.2 (C-3"), 64.8 (C-5"), 39.9 (3'-$N(CH_3)_2$), 49.1 (3"-OCH_3), 44.3 (C-2), 34.8 (C-2"), 29.9 (C-4'), 22.9 (5'-CH_3), 18.5 (5"-CH_3), 10.0 (C-15), 9.5 (4-CH_3).

MS (ES^+) m/z (%): 936.3.

Example 7

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(p-toluenesulfonyl)carbamoyl]-9a-aza-9a-homoerythronolide A

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A (1.0 g, 0.00173 moles) was dissolved in toluene (25 ml) and p-toluenesulfonylisocyanate (about 0.34 mg, 0.00173 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(p-toluenesulonyl)carbamoyl]-9a-aza-9a-homoerythronolide A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol : ammonia = 90 : 9 : 1.5.

IR (KBr)/cm^{-1}: 1726, 1171, 1129, 1075.

MS (ES^+) m/z (%): 774.9.

Example 8

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(4-chlorobenzenesulfonyl)-carbamoyl]-9a-aza-9a-homoerythronolide A

Analogously to the process described in Example 1, 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A (2.54 g, 0.0046 moles) was dissolved in toluene (50 ml) and 4-chlorobenzenesulfonylisocyanate (1.0 g, 0.00459 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(4-chlorobenzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythronolide A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol = 7 : 3.

IR (KBr)/cm^{-1}): 1725, 1174, 1133, 1078.

MS (EI^+) m/z (%): 784.7.

Example 9

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(4-fluorobenzenesulfonyl)-carbamoyl]-9a-aza-9a-homoerythronolide A

Analogously to the process described in Example 1, 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A (1.0 g, 0.00173 moles) was dissolved in toluene (25 ml) and 4-fluorobenzenesulfonylisocyanate (0.36 g, 0.00173 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(4-fluorobenzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythronolide A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol = 7 : 3.

IR (KBr)/cm^{-1}: 1727, 1174, 1129, 1076.

MS (EI^+) m/z (%): 778.8.

Example 10

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)-carbamoyl]-9a-aza-9a-homoerythronolide A

Analogously to the process described in Example 1, 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A (3.055 g, 0.0055 moles) was dissolved in toluene (25 ml) and benzenesulfonylisocyanate (1.0 g, 0.0055 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(benzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythronolide A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol = 7 : 3.

IR (KBr)/cm^{-1}: 1728, 1176, 1128, 1077.

MS (ES^+) m/z (%): 760.7.

Example 11

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(o-toluenesulfonyl)-carbamoyl]-9a-aza-9a-homoerythronolide A

Analogously to the process described in the Example 1, 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A (2.84 g, 0.0051 moles) was dissolved in toluene (40 ml) and o-toluenesulfonylisocyanate (1.0 g, 0.0046 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one

hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(o-toluenesulfonyl)carbamoyl]-9a-aza-9a-homoerythronolide A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol = 7 : 3.

IR (KBr)/cm^{-1}: 1728, 1173, 1129, 1075.

MS (EI^+) m/z (%): 774.7.

Example 12

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(2-chlorobenzenesulfonyl)-carbamoyl]-9a-aza-9a-homoerythronolide A

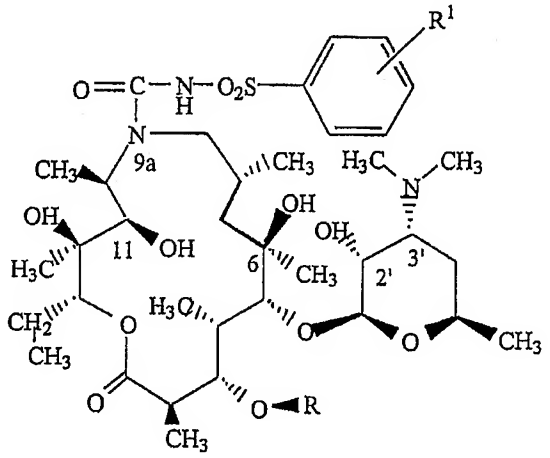
Analogously to the process described in Example 1, 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A (2.65 g, 0.00459 moles) was dissolved in toluene (50 ml) and a toluene suspension of 2-chlorobenzenesulfonylisocyanate (1.0 g, 0.00459 moles) was added dropwise at a temperature from 0°C to 5°C. After stirring the reaction mixture for one hour at the same temperature, the formed crystals of the crude product were sucked off. The isolation of the pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-(2-chlorobenzenesulfonyl)carbamoyl]-9a-aza-9a-homoerythronolide A was performed by chromatography on a silica gel column in a solvent system methylene chloride : methanol = 7 : 3.

IR (KBr)/cm^{-1}: 1728, 1170, 1125, 1071.

MS (ES^+) m/z (%): 794.1.

Claims

1. 9a-N-[N'-(Phenylsulfonyl)carbamoyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A of the general formula **1**:



1

wherein R^1 denotes H, C_1-C_4 alkyl or halogen and R denotes H or cladinosyl radical, and their pharmaceutically acceptable addition salts with inorganic or organic acids.

2. A compound according to claim 1, **characterized in that** R^1 denotes H and R denotes cladinosyl radical.

3. A compound according to claim 1, **characterized in that** R^1 denotes CH_3 in p-position and R denotes cladinosyl radical.

4. A compound according to claim 1, **characterized in that** R^1 denotes CH_3 in o-position and R denotes cladinosyl radical.

5. A compound according to claim 1, **characterized in that** R^1 denotes Cl in p-position and R denotes cladinosyl radical.

6. A compound according to claim 1, **characterized in that** R^1 denotes Cl in o-position and R denotes cladinosyl radical.

7. A compound according to claim 1, **characterized in that** R^1 denotes F in p-position and R denotes cladinosyl radical.

8. A compound according to claim 1, **characterized in that** R^1 and R denote H.

9. A compound according to claim 1, **characterized in that** R^1 denotes CH_3 in p-position and R denotes H.

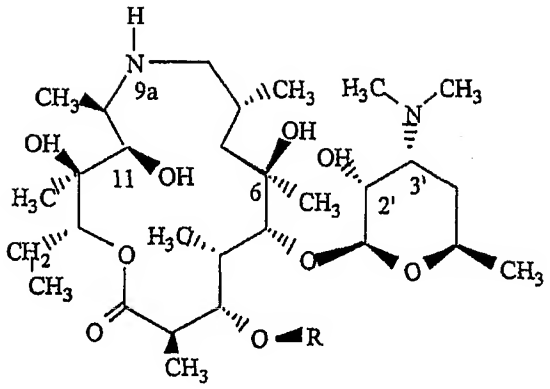
10. A compound according to claim 1, **characterized in that** R^1 denotes CH_3 in o-position and R denotes H.

11. A compound according to claim 1, **characterized in that** R^1 denotes Cl in p-position and R denotes H.

12. A compound according to claim 1, **characterized in that** R^1 denotes Cl in o-position and R denotes H.

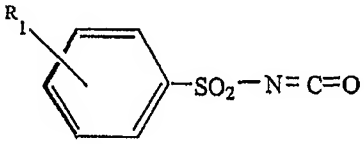
13. A compound according to claim 1, **characterized in that** R^1 denotes F and R denotes H.

14. A process for the preparation of 9a-N-[N'-(phenylsulfonyl)carbamoyl] derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A and of 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A of the general formula **1**, wherein R^1 denotes H, C_1-C_4 alkyl or halogen and R denotes H or cladinosyl radical, **characterized in that** 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A or 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A of the general formula **2**



2

is reacted with phenylsulfonylisocyanates of general formula **3**



3

wherein R^1 denotes the meanings given in claim 1, in toluene, xylene or some other aprotic solvent at a temeperature from 0°C to 110°C.

15. A pharmaceutical composition, **characterized in that** it comprises a pharmaceutically acceptable carrier and an antibacterially effective amount of compounds according to claim 1.

16. A compound according to any of the claims 1-13, **characterized in that** it is used for the preparation of pharmaceutical preparations for the treatment of bacterial infections.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 September 2002 (06.09.2002)

PCT

(10) International Publication Number
WO 2002/068438 A3

(51) International Patent Classification[7]: C07H 17/00, A61K 31/70, A61P 31/04

(21) International Application Number: PCT/HR2002/000010

(22) International Filing Date: 27 February 2002 (27.02.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P20010146A 28 February 2001 (28.02.2001) HR

(71) Applicant *(for all designated States except US)*: **PLIVA D.D.** [HR/HR]; Ulica Grada Vikovara 49, HR-10000 Zagreb (HR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUJUNDZIC, Nedjeljko** [HR/HR]; Slavenskog 4, HR-10000 Zagreb (HR). **BUKVIC KRAJACIC, Mirjana** [HR/HR]; Slavenskog 8, HR-10000 Zagreb (HR). **DUMIC, Miljenko** [HR/HR]; Ivane Brlic Mazuranic 4, HR-10000 Zagreb (HR). **HASENOHRL, Andrea** [HR/HR]; Dragozetnicka 11, HR-10000 Zagreb (HR).

(74) Agent: **PLIVA D.D.**; Ulica Grada Vikovara 49, HR-10000 Zagreb (HR).

(81) Designated States *(national)*: AU, BA, CN, CZ, EE, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, PL, RO, SI, SK, TR, UA, US, YU, ZA.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

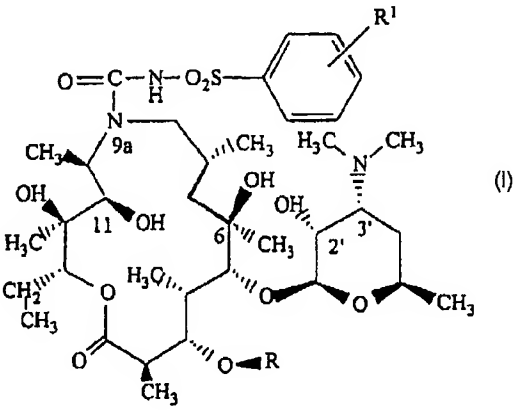
Published:
— *with international search report*

(88) Date of publication of the international search report:
26 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2002/068438 A3

(54) Title: 9A-N-[N'-(PHENYLSULFONYL)CARBAMOYL] DERIVATIVES OF 9-DEOXO-9-DIHYDRO-9A-AZA-9A-HOMOERYTHROMYCIN A AND OF 5-O-DESOSAMINYL-9-DEOXO-9-DIHYDRO-9A-AZA-9A-HOMOERYTHRONOLIDE A



(I)

(57) Abstract: The invention relates to 9a-N[N'-(phenylsulfonyl)carbamoyl] derivatives of 9-deoxo-9-dihydro-9a-aza-homoerythromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerythronolide A, novel semisynthetic macrolide antibiotics from the class of azalides, of the general formula (I) wherein R^1 denotes H, C_1-C_4alkyl or halogen and R denotes H or cladinosyl radical, to their pharmaceutically acceptable addition salts with inorganic or organic acids, to intermediates and methods for their preparation, to a process for the preparation of pharmaceutical compositions as well as to the use of pharmaceutical compositions in the treatment of bacterial infections.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HR 02/00010

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/00 A61K31/70 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 66603 A (MARU & SCARON ;MUTAK STJEPAN (HR); KUJUND & ZCARON (HR); MAR & SCA) 9 November 2000 (2000-11-09) the whole document	1,14-16
A	EP 0 657 464 A (PLIVA PHARM & CHEM WORKS) 14 June 1995 (1995-06-14) cited in the application the whole document	1,14-16
A	US 4 826 820 A (BRAIN EDWARD G) 2 May 1989 (1989-05-02) column 37, lines 31-47	1,14-16
A	US 4 434 000 A (MAHONEY MARTIN D ET AL) 28 February 1984 (1984-02-28) abstract	1,14-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2002	14/05/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fitz, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HR 02/00010

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0066603	A	09-11-2000	HR	990130 A1	31-10-2001
			AU	4135000 A	17-11-2000
			BR	0010231 A	19-02-2002
			EP	1175429 A1	30-01-2002
			WO	0066603 A1	09-11-2000
			NO	20015346 A	01-11-2001
EP 0657464	A	14-06-1995	HR	931480 A1	31-08-1996
			AT	144778 T	15-11-1996
			BG	61571 B1	30-12-1997
			BG	99242 A	29-09-1995
			CA	2137395 A1	09-06-1995
			CN	1109890 A ,B	11-10-1995
			CZ	9403082 A3	12-07-1995
			DE	69400817 D1	05-12-1996
			DE	69400817 T2	22-05-1997
			EP	0657464 A1	14-06-1995
			ES	2096401 T3	01-03-1997
			HU	69283 A2	28-09-1995
			JP	3131546 B2	05-02-2001
			JP	7252292 A	03-10-1995
			PL	306154 A1	12-06-1995
			RO	113854 B1	30-11-1998
			RU	2131878 C1	20-06-1999
			SI	9400434 A	30-06-1995
			SK	146994 A3	11-07-1995
			US	5629296 A	13-05-1997
US 4826820	A	02-05-1989	AU	6186286 A	05-03-1987
			DK	406586 A	01-03-1987
			EP	0216169 A2	01-04-1987
			GR	862216 A1	31-12-1986
			JP	62084095 A	17-04-1987
			PT	83254 A ,B	01-09-1986
			ZA	8606443 A	29-07-1987
US 4434000	A	28-02-1984	US	4787932 A	29-11-1988